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August 20, 2003

The Honorable Marianne Lamont Horinko
Acting Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program

Re: Response to Comments and Amendments to Pine Chemicals Association, Inc. Test plan for Rosin Esters

Dear Ms. Horinko:

The Pine Chemicals Association, Inc., HPV Task Force (PCA) has reviewed the comments on its Test Plan for Rosin Esters from Environmental Defense (ED) and the Environmental Protection Agency (EPA) dated August and December 2002, respectively. We are pleased to offer the following response.

We begin by noting that PCA previously addressed the comments of the People for the Ethical Treatment of Animals (PETA) on the rosin esters test plan in a letter dated October 31, 2002. Because PETA's comments addressed concerns related to our treatment of the rosin esters, rosin adducts, and rosins categories, as well as our overall approach to animal welfare, PCA believed a separate response was appropriate. We direct your attention to that letter posted on EPA's website as we will not reiterate our responses to PETA here.

RESPONSE TO COMMENTS & AMENDMENTS TO TEST PLAN

Categorization of Substances / Selection of Test Materials

PCA proposed to group seven substances in its Test Plan for Rosin Esters, using two compounds as category representatives – rosin pentaerythritol ester (CAS # 8050-26-8) and rosin partially hydrogenated methyl ester (CAS # 8050-15-5). PCA selected these two substances to represent the molecular weight extremes of the seven substances in this category. ED agreed with our category and representative test substances. EPA also agreed with the chemical category and the use of rosin pentaerythritol ester (PE) as a

representative test substance. Although EPA agreed with PCA's approach for choosing representative substances, the Agency recommended that rosin methyl ester (instead of rosin partially hydrogenated methyl ester) should be used as the second representative test substance. EPA believed that rosin methyl ester – as an unsaturated ester – may undergo epoxidation during metabolism and therefore be more toxicologically active. Although this is a hypothetical possibility -- because some compounds can undergo epoxidation in biological systems -- there is no evidence in the literature that rosin methyl ester would be susceptible to epoxidation in a biological system. Furthermore, since the $LD_{50's}$ of both the rosin methyl ester and rosin partially hydrogenated methyl ester are >2000 mg/kg, there is no basis for assuming that the rosin methyl ester would be more toxic. Further, it also should be noted that the relative production and commercial importance of rosin, partially hydrogenated methyl ester is far greater than that of the rosin methyl ester.

Finally, we note that the lengthy delay in receiving EPA's comments on the Rosin Ester Test Plan. PCA submitted this test plan to EPA on January 18, 2002. EPA published its comments December 5, 2002, almost a year later. In the meantime, it was necessary for us to proceed with the proposed testing of all of the substances in this group, including rosin, partially hydrogenated methyl ester, to meet our contractual obligations with the testing laboratory and not to lose our scheduled starting dates.

Physicochemical Properties and Environmental Fate

Melting Point

In comments on physicochemical properties, EPA acknowledged that *"melting points values cannot be determined because the compounds in this category are mixtures and either will not give a sharp melting point when heated or will decompose before they melt."* However, EPA requested that PCA identify which rosin esters decompose upon heating and which ones have a broad softening point and provide the softening points in the robust summaries.

The two methyl esters in this category are liquids at room temperatures, and rosin, diethylene glycol ester is a viscous liquid. Therefore, the softening point for these three substances is irrelevant. However, PCA will provide softening points in the final robust summaries for the four substances in this category that are solids at room temperature.

Boiling Point

With respect to the boiling point, EPA commented that according to OECD Guideline 103 *"measurements at reduced pressure may be appropriate for substances with a high boiling point and substances which decompose at elevated temperatures."* The relevance of conducting this kind of testing for any HPV substance -- much less for the substances in this category -- is highly questionable when the test data are to be reported at ambient conditions. All of the substances in this category will decompose well before they boil at ambient pressure. Data on boiling points at elevated temperatures and reduced pressure (i.e., below ambient) would only be relevant for designing fractional distillation processes. Consequently, PCA will undertake no determination of boiling points for any of the substances in this category.

Vapor Pressure

For vapor pressure, EPA suggested that if calculated vapor pressures are < 7.5 x 10^{-5} mm Hg they may be acceptable under OECD Guideline # 104. As demonstration of this, the Agency supposedly provided EPIWIN estimates of 6.65 x 10^{-5} mm Hg for rosin, methyl ester (CAS# 68186-14-1) and 1.44 x 10^{-5} mm Hg for rosin, partially hydrogenated, methyl ester (CAS# 8050-15-5). However, neither of these calculated vapor pressures could be for these two complex mixtures because EPIWIN is incapable of performing estimates for such mixtures. Rather, these values could only be for some unidentified component of the mixture. Furthermore, we note that both estimates, although not representative of the mixtures themselves, suggest that the vapor pressures of individual components would be less than the OECD threshold. Table 1 illustrates this point for the methyl esters of six representative rosin acids. Because EPIWIN cannot be used to estimate the vapor pressure for complex mixtures such as rosin, methyl ester or rosin, partially hydrogenated, methyl ester, it is the conclusion of PCA that a determination of the vapor pressures for any of the multi-component substances in this category is impracticable.

Table 1. Estimated vapor pressures for six rosin acid methyl esters.

Rosin acid methyl ester	**EPIWIN estimated vapor pressure**
Abietic acid	6.6 x 10^{-5}
Neoabetic acid	5.8 x 10^{-6}
Palustric acid	6.06 x 10^{-6}
Levopimaric acid	6.65 x 10^{-5}
Isopimaric acid	9.0 x 10^{-6}
Sandaracopimaric acid	9.0 x 10^{-6}

Photodegradation

EPA suggested that PCA should estimate photodegradation based on an estimated vapor pressures for rosin, methyl ester (CAS# 68186-14-1) and rosin, partially hydrogenated methyl ester (CAS # 8050-15-5) of 6.65 x 10-5 mm Hg and 1.44 x 10-5 mm Hg, respectively. However, as noted above, it does not appear that these are the vapor pressures for either rosin, methyl ester or rosin, partially hydrogenated methyl ester, but rather the vapor pressures for two (unidentified) components that are part of these complex mixtures. There is little reason for EPA to assume that the vapor pressure of one substance in a multi-substance mixture is representative of the entire mixture. Consequently, after careful consideration of this issue, it is the conclusion of PCA that determination of the potential photodegradation of any of the multi-component substances in this category is impracticable.

Fugacity

In commenting on a determination of fugacity, EPA disagreed with the statement from the test plan that *"due to the inability to provide usable inputs to the required model, no determination of transportation and distribution between environmental*

compartments will be undertaken for rosin esters." EPA suggested that *"by using structurally analogous compounds that represent the chemical mixtures for each of the 7 classes, the fugacity calculations are possible."* We should note that the rosin ester category of substances is not comprised of 7 classes of substances, but rather 7 different rosin esters. Each of these mixtures is a combination of various diesters, triesters and small amounts of unreacted resin acids. There is further complexity due to the presence of numerous resin acids, including abietic, dehydroabietic, neoabetic, pimaric, sandarcopimaric, communic, palustric, and isopimaric, all of which are esterified. Because there is no single compound that is representative of the mixture, any inputs into a fugacity model based upon a single compound will yield a result that is not representative of the mixture.

Moreover, there are various mathematical models for estimating fugacity. One of the most frequently referenced models is the one used by the Canadian Environmental Centre, referenced as "Multimedia Environmental Models; The Fugacity Approach," by D. Mackay, Lewis Publishers, CRC Press (1991). Even the simplest of these models requires estimates of solubility, vapor pressure and octanol/water partition coefficient to estimate fugacity for a single component. For a complex class 2 substance such as rosin, estimates of any one of these physical parameters for the various known components would span a range of more than an order of magnitude (as we noted above in the EPIWIN estimates of vapor pressure). When combining three or more parameters with equally variable ranges to derive estimates for the different environmental media, the variability in the estimate for any given medium would grow geometrically to more than three of more orders of magnitude. This would seem to render the estimates rather useless for any practical purpose. Add to this the additional fact that there is variability in the actual chemistry, i.e.: triester, diester and monoester, and the permutations become unmanageable. Thus, we conclude that for such complex mixtures as rosin esters, the mathematical models relying upon estimates for individual components are of little practical use in predicting environmental fate.

For these reasons, PCA will not undertake to determine the transportation and distribution of rosin esters between environmental compartments.

Ecotoxicity Tests

EPA disagreed with the proposal in the test plan to conduct acute testing on fish, daphnia and algae for the two representative substances (i.e., rosin PE ester and rosin, partially hydrogenated methyl ester) based on the unsubstantiated assertion that *"chronic toxicity is likely to occur with these substances."* Rather, EPA suggested that only one test be conducted on a different compound (i.e., rosin, methyl ester, CAS# 68186-14-1) in a 21-day daphnia test, reasoning that the low water solubility and estimated log Kow < 7.5 would somehow translate into greater toxicity. As noted in the Test Plan, none of these complex substances have partition coefficients that can be represented by a single value. For example, the range of log K_{ow} values for rosin, PE ester and rosin partially hydrogenated methyl ester is 4.6-7.3 and 6.4-7.6, respectively. In comparison, the range of log K_{ow} values for rosin, methyl ester is 4.9-7.6, representing essentially no difference in the log K_{ow} values for the two representative substances and the substance suggested by EPA.

Furthermore, EPA's claim *that "Because the calculated log Kow for CAS No. 68186-14-1 is lower than that for CAS No. 8050-15-5 it is the preferred test substance"* is questionable for several reasons. For these kinds of complex mixtures, estimation of parameters such as K_{ow} is not possible, and, as described above, these mixtures exhibit a range of K_{ow} values rather than a single value. Finally, there does not appear to be any basis for EPA's claim that only rosin, methyl ester would exhibit aquatic toxicity and that *"other category members will not show aquatic acute or chronic effects based on their physiochemical properties."* Consequently, after consideration of EPA's comments, PCA does not intend to amend its test plan with regard to the proposed ecotoxicity testing. It should be noted that the ecotoxicity testing has been conducted in accordance with the recommendations found in the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD 2000).

In addition, given the extremely low solubility of both test materials, EPA's recommendation for a 21-day test using a flow-through method for even one of these substances would be impracticable. Based on the amount of water that would be required and the difficulty in performing the necessary serial analytical measurements, a flow-through test for rosin, methyl ester is simply not feasible. Thus, chronic aquatic toxicity testing in daphnia will not be undertaken for this substance.

Human Health Effects

Acute Toxicity

EPA noted that Table 1 in the test plan indicated that there was acute toxicity data for rosin, glycerol ester, but no robust summary for this data. After looking into this, we determined that Table 1 was in error, i.e., there is no acute toxicity data for this compound. Table 1 has been changed to reflect this and is appended to this letter.

Both EPA and ED disagreed with PCA's proposal to conduct acute toxicity testing on rosin pentaerythritol ester since the substance was already the subject of both 90-day and lifetime cancer studies in rodents, resulting in a maximally tolerated dose of 5000 mg/kg. PCA understands and appreciates the logic supporting this suggestion. However, at the time that available data were being reviewed we did not appreciate from the available guidance documents that EPA would accept chronic data for acute purposes.

Genotoxicity

EPA disagreed with what they incorrectly interpreted in our test plan as a proposal to conduct *in vivo* genetic toxicity testing for rosin partially hydrogenated methyl ester. The Agency commented that *in vitro* genetic toxicity testing should be used under the HPV program *"unless known chemicals preclude its use."* We note that the plan did not state that *in vivo* testing would be used. Rather, it stated that tests in bacteria (OECD 471) and mammalian cell (OECD 476) would be conducted on this compound. Both of these tests are conducted *in vitro*.

EPA disagreed with PCA's reliance on a negative 2-year carcinogenicity study on rosin, PE ester (CAS# 8050-26-8) to fulfill the genotoxicity endpoint. This was based on EPA's contention that this study failed to meet certain criteria for a cancer bioassay including group size, and the use of multiple exposure concentrations. While these

observations might be correct, as described in the robust summary, the exposure was adequate to produce benign tumors in both the control and exposed groups. These results suggest that the dose level used was adequate to have produced a carcinogenic response if this substance were capable of causing malignant tumors.

In addition, EPA's comments also disagreed with the statement from the rosin esters test plan that *"since the purpose of in vitro bacterial and mammalian mutagenicity tests is to determine if a chemical might have the potential to be a direct-acting DNA reactive carcinogen, the negative carcinogenicity studies eliminate the need to test for potential genotoxicity."* The comments then go on to list a number of genetic diseases and conditions (e.g., Down's syndrome, cystic fibrosis, hemophilia, sickle-cell anemia, allergies, mental retardation, etc.) with the implication that mutagenicity testing is able to predict the ability of a chemical to cause these adverse outcomes. There is no evidence that the two genotoxicity screening tests that comprise the SIDS battery of tests (i.e., bacterial mutation and chromosomal aberration) have this ability. The likelihood that such testing would predict the non-cancer endpoints noted in EPA's comments is also tempered by the following observation in Casarett & Doull's textbook on Toxicology (1996): *"No clear evidence exists for the induction of heritable alterations by radiation or chemicals in human germ cells."*

Finally, in the early stages of the HPV program, there was uncertainty about the format in which robust summary data would be submitted to EPA. In a meeting with Dr. Oscar Hernandez to discuss this issue, the summarized rosin data were used to illustrate a possible robust summary format. The above statement concerning the ability of negative carcinogenicity data to eliminate the need to test for potential genotoxicity was included in the summarized data as part of this discussion. While Dr. Hernandez noted that mutagenicity testing might indicate the potential for possible endpoints other than cancer, he readily agreed that for purposes of the HPV program, a negative cancer bioassay was a suitable surrogate for genotoxicity testing. Accordingly, PCA will not undertake to test rosin, PE ester (CAS # 8050-26-8) for bacterial gene mutations and chromosomal aberration. The headings on the summary tables in the test plan will be changed as suggested to reflect the more accurate designations "gene mutation" and "chromosomal aberrations" rather than the bacterial and non-bacterial assays.

In reviewing the three robust summaries for the negative genotoxicity results for rosin, glycerol ester (CAS# 8050-31-5), EPA concluded that the studies were inadequate since none tested concentrations up to the limits of toxicity or solubility. However, the Food and Drug Administration (FDA) has judged that these results are adequate to support a Generally Recognized as Safe ("GRAS")-like status for this substance (CFR § 172.735 and 172.615).

In commenting on the reproductive toxicity endpoint, EPA noted that the reproductive toxicity data in Table 1 of the test plan needed to be re-categorized due to the fact "*that this endpoint has not been adequately addressed for any of these category members for the purposes of the HPV Challenge Program because only repeated-dose toxicity studies are available with no existing adequate developmental toxicity data…*" It does not appear that EPA carefully reviewed the test plan since this issue was discussed in some detail. As noted in the plan, the SIDS guidelines for the reproduction toxicity endpoint clearly state that, *"when a 90-day repeated dose study is available and*

demonstrates no effects on the reproductive organs, in particular the testes, then a developmental study can be considered as an adequate test to complete information on reproduction/developmental effect." Of the seven rosin esters in this category, four have been tested in 90-day repeat dose studies including rosin, pentaerythritol ester; rosin, glycerol ester; rosin, hydrogenated, glycerol ester; and rosin, hydrogenated, pentaerythritol ester. In addition, rosin pentaerythritol ester has also been tested in a two-year bioassay. All of the 90-day studies and the two-year study included histopathology of reproductive organs (i.e., testes, ovaries, and uterus). The results of these tests are described in the test plan as well as in the robust summaries.

Based on these data, it was concluded that the database of studies for the rosin esters satisfies the SIDS reproductive toxicity endpoint for one of the representative compounds. A developmental toxicity study using OECD Method 421 has been conducted on rosin, pentaerythritol ester to complete the information on developmental toxicity for this substance. Because there were no reproductive/developmental data for the other representative compound, (rosin, partially hydrogenated, methyl ester), this substance has been tested for reproductive/developmental toxicity (in conjunction with repeat dose toxicity) using OECD method 422.

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PCA appreciates the comments from EPA and ED and the opportunity to respond. We look forward to sharing the data generated pursuant to the Test Plan.

Respectfully submitted,

Walter L. Jones
President & COO

Table 1
Matrix of Available Adequate Data and Proposed Testing
On Rosin Esters *

Chemical and CAS #	Required SIDS Endpoints										
	Partition Coef.	**Water Sol.**	**Biodeg.**	**Acute Fish**	**Acute Daph.**	**Acute Algae**	**Acute oral**	**Repeat Dose**	**In vitro gene mutation**	**In vitro Chrom. Ab.**	**Repro/ Develop**
Rosin, penta-erythritol ester 8050-26-8	Test	Test	Test	Test	Test	Test	Test	Adeq.	Adeq.	Adeq.	Adeq. Repro; Test Develop.
Rosin, glycerol ester 8050-31-5	Test	Test	Test	C	C	C	C	Adeq.	Adeq.	Adeq.	Adeq. Repro; C Develop.
Rosin, diethylene glycol ester 68153-38-8	Test	Test	Test	C	C	C	C	C	C	C	C
Rosin, methyl ester 68186-14-1	Test	Test	Test	C	C	C	Adeq.	C	C	C	C
Rosin, hydrogenated glycerol ester 65997-13-9	Test	Test	Test	C	C	C	C	Adeq.	C	C	Adeq. Repro; C Develop
Rosin, hydrogenated penta-erythritol ester 64365-17-9	Test	Test	Test	C	C	C	C	Adeq.	C	C	Adeq. Repro; C Develop
Rosin, partially hydrogenated methyl ester 8050-15-5	Test	Test	Adeq.	Test	Test	Test	Adeq.	Test	Test	Test	Test Test

Adeq. Indicates adequate existing data
Test Indicates proposed testing
C Indicates category read-down from existing or proposed test data on rosin, pentaerythritol ester or rosin, partially hydrogenated, methyl ester

***** No testing will be conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation and transport and distribution between environmental compartments as explained in the test plan.